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Exploring the First Steps of Aβ16-22 Protofibril Disassembly by N-Methylated Inhibitors

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Alzheimer's disease is characterized by the self-assembly of the Aβ(1-40)/(1-42) peptides. The design of efficient inhibitors is particularly challenging because the structures of the toxic Aβ species are transient in character and the modes of action of current inhibitors on Aβ oligomers are unknown. We know that N-methylated Aβ16-22 peptides (mAβ16-22) effectively inhibit fibrillogenesis and disassemble existing fibrils in vitro. In this work we report molecular dynamics (MD) and replica exchange molecular dynamics (REMD) simulations using the coarse-grained OPEP force field on a preformed protofibril of six Aβ16-22 peptides with either four copies of Aβ16-22 or four copies of mAβ16-22. While MD trajectories of 100 ns do not reveal any significant differences between the two systems, REMD simulations help understand the first steps of Aβ16-22 protofibril disassembly by N-methylated inhibitors.

1 Introduction

Alzheimer's disease is a fatal neurodegenerative disease characterized by the aggregation of amyloid-β peptides. There is increasing evidence that the oligomers of Aβ are themselves cytotoxic[1] and the hydrophobic region 16-22 is critical for aggregation. Several inhibitors have been designed in order to inhibit the aggregation process[2]. N-methylated inhibitors such as mAβ16-22 are known to prevent the growth of the fibrils and disassemble fibrils. However the mechanism of action of this inhibitor is not determined. Our work consists on studying the early steps of the inhibition using a preformed protofibril in interaction with either Aβ16-22 and mAβ16-22 (called in the text Aβ and mAβ) by MD and REMD simulations. Our results show that N-methylated peptides disassemble the preformed fibril by three mechanisms.

2 Materials and Methods

We use the coarse grained force field `OPEP` (*Optimized Potential for Efficient peptide-structure Prediction*) in its last version[3], which describes the short-range as well as long-range interactions of proteins, in a reduced representation. The initial structure of all our simulations is shown in figure 1 : it consists of a preformed bi-layer of 6 Aβ, and 4 free Aβ or mAβ. In mAβ, the (-N**H**) group of residues (`Leu 17`, `Phe 19` and `Ala 21`) is replaced by (-N**CH3**). Each system is minimized and equilibrated at the desired temperature for 1 ns. MD simulations[4] of 100 ns are realized at constant temperature (330 K), using Berendsen's thermostat and an integration time step of 1fs. For the REMD simulations, we used 16 replicas for temperatures ranging from 280 to 440 K, exchanges between neighboring replicas are attempted every 7.5 ps. Periodic boundary conditions are using for the

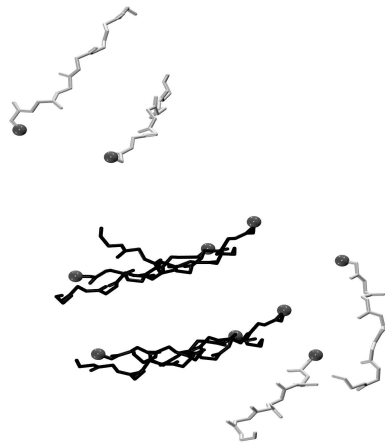

Figure 1. The starting structure for simulations : the preformed Aβ bi-layer (in black) in interaction with four copies of Aβ or mAβ (in gray). The N-terminal end of each peptide is indicated with a sphere.

systems, leading to a concentration of around 50 μM. The time of the REMD simulations is of 30 ns, noting that our purpose is to characterize the first steps of the inhibition mechanism, and not the thermodynamical behavior of the systems under equilibrium, requiring much longer simulation times. For the analysis, we calculate the nematic order parameter[5] P_2on the 6 peptides of the preformed fibril F1-F6, if $P_2 = 1$ then the system is fully parallel or antiparallel, otherwise if $P_2 = 0$ it is disordered.

3 Destabilization of the Fibril by N-Methylated Peptides

100 ns MD simulation of the system 10Aβ16-22 shows an average Cα-RMSD (calculated on the starting structure) of 2.7 Å for the first layer and 1.8 Å for the second one. Identical values are obtained for the simulation of 6Aβ + 4mAβ. Similarly no differences are found for the P2 values and the β-sheet content between the two systems, providing strong evidence that within the timescale explored, no difference in the aggregation process can be identified upon N-methylation. This is consistent with simulations using mAβ16-20[6]. To overcome the sampling encountered by MD simulations, we studied the effect of N-methylation by REMD. Figure 2.a shows the number of clusters and the P2-value averaged at every temperature for both the systems studied. These results show an increase of 32 % of the number of clusters and a decrease of 36.7 % of the P2-value in the presence of mAβ.

4 Binding of the N-Methylated Peptides to the Protofibril

In order to characterize at atomic level the effect of the inhibition upon the preformed fibril, we realized a clusterisation at all tempertaures using a RMSD cutoff of 3 Å on the six peptides F1-F6. These results show that the N-methylated peptides desorganize the protofibril at every temperature. Looking at the structures obtained at 280 and 315 K, we identified three mechanisms of binding between the N-methylated peptides and Aβ. Panels

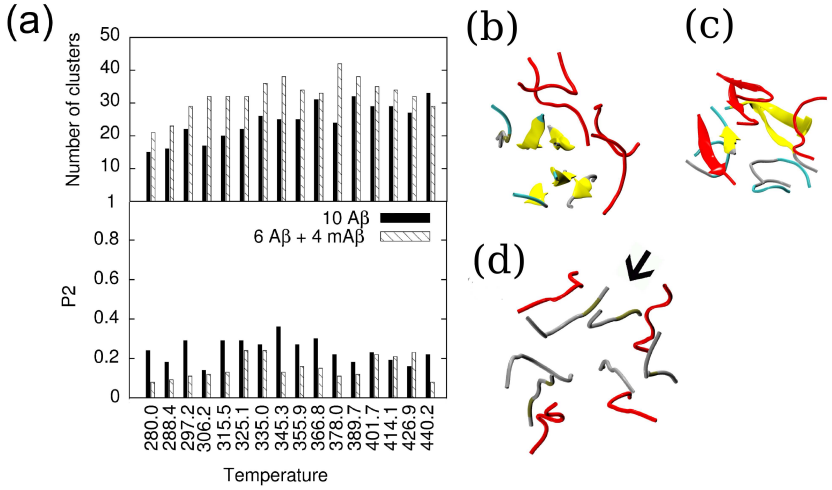

Figure 2. (a) Temperature-dependant properties of the peptides F1-F6 in 10 Aβ and 6Aβ+4mAβ simulations. (b,c) Center of the most populated clusters at 280 K for 10Aβ (b) and 6Aβ+4mAβ (c). (d) Center of one cluster at 315 K for 6Aβ+4mAβ. The N-methylated peptides are shown in red, the six preformed peptides F1-F6 use the following color code : yellow for β-sheet, grey for coil and blue for turn.

2.b and 2.c show the centers of the most populated clusters C1 with and without mAβ at 280 K. The Cα-RMSD calculated with respect to the preformed fibril are of 2.7 and 8.5 Å, respectively. In the structure of C1 in 2.c, two modes of binding are observed : on the top of an Aβ-sheet and a β-sheet formed between mAβ and Aβ peptides. Panel 2.d shows one cluster of the 6Aβ+4mAβ simulation at 315 K, presenting the third mode of interaction characterized by one intercalated mAβ and two Aβ peptides sequestered by two mAβ (see arrow in figure 2.d).

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